Advanced Methods for Dose–Response Assessment: Bayesian Approaches—Final Report

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Abstract

Resources for the Future (RFF), in conjunction with the U.S. Environmental Protection Agency, the Society for Risk Analysis, and the Electric Power Research Institute, held a workshop Sept. 18–20, 2000, at the RFF Conference Center in Washington, DC. The intent was to discuss how Bayesian approaches could be useful in improving techniques for estimating exposure–response functions. Ten distinguished scholars from a range of fields (medical biostatistics, decision sciences, environmental engineering, and toxicology) served as faculty. Approximately 80 people attended the workshop. Bayesian methods have been applied to a variety of problems in biomedical research and environmental risk analysis, including design of clinical trials, estimation of exposures to humans and local environments, and, in a few cases, estimation of exposure–response functions. Bayesian methods offer two signal advantages: their use requires careful analysis of problem logic, which has intrinsic utility, and disparate data can be incorporated into calculations. Although application of formal Bayesian analysis can be computationally challenging, widely available computer programs now greatly reduce this burden. Participants identified several factors that may impede the dissemination of Bayesian approaches among practitioners of dose–response assessment and made some recommendations for overcoming these hurdles.

- EPA, other regulatory agencies that use dose–response assessment as part of their processes, and the private sector all should take steps to foster the use of Bayesian approaches.
- EPA and other agencies should work to persuade professional societies (for example, Society for Risk Analysis, Society of Toxicology) to seek out and recognize meritorious analyses that use Bayesian approaches.
- EPA and private-sector organizations should consider sponsoring research into using Bayesian approaches, demonstration analyses that use them, and using the results of this work to help educate peers in the risk analysis and toxicology professions.
- EPA should request all staff and contractor scientists who develop mathematical models to use Bayesian techniques to calibrate models.
- EPA should consider ways to inform its staff, contractors, and the research community as to the utility of Bayesian analyses.
- EPA should consider improving its research planning by making use of Bayesian techniques (including value-of-information analyses).

Key Words: Bayesian analysis; dose–response; regulation; risk assessment; arsenic

Contents

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Bayesian analysis is an important tool now widely used in many domains, including some parts of risk analysis. It provides the foundation for the technical field of decision analysis.[1] Although the method originated in the eighteenth century, the present widespread application has followed the development of modern computing capabilities; formal application requires complex probability computations. The fundamental concept of Bayesian logic is that we improve our knowledge by using new information to modify what we knew before. (Occasionally, new information overturns previous conclusions; but usually, the result is reduced uncertainty.) Some philosophers suggest that Bayesian logic—the approach, not necessarily involving actual calculation of probabilities—best describes the scientific method.[2]

The U.S. Environmental Protection Agency (EPA) asked Resources for the Future (RFF) to organize a workshop on the potential for Bayesian approaches to contribute to progress in dose–response assessment. The Electric Power Research Institute joined in sponsoring this workshop, which was organized jointly by RFF, EPA, and the Society for Risk Analysis. It was held in RFF's conference facilities Sept. 18–20, 2000. This report describes the proceedings of the workshop and records some suggestions that may facilitate the adoption of more formal Bayesian approaches within the subdiscipline of human health risk assessment.

Description of the Program

The workshop agenda appears as Appendix I. Appendix II lists the workshop faculty and panelists, and Appendix III gives the attendees. Some useful websites are provided in Appendix IV, and Appendix V is a list of some books and papers that describe relevant uses of Bayesian analysis.

Early on, the workshop's advisory committee[3] raised the issue of just where this workshop would fall within the spectrum of Bayesian approaches. At one end, there stand the intuitive (and usually unstructured) approaches that most scientists absorb during their apprenticeships in science—these approaches are not usually accompanied by an understanding of the underpinning formal logic. At the other end stand the formalized decisionmaking procedures that incorporate decision criteria framed in

[1] D. Warner North. A tutorial introduction to decision theory. *IEEE Transactions on Systems Science and Cybernetics* **4**(3): 200–210 (1968).

[2] C. Howson and P. Urbach. *Scientific Reasoning: The Bayesian Approach.* La Salle, IL: Open Court Publishing Co. (1989).

[3] The advisory committee included Alison Cullen, Victor Hasselblad, Annie Jarabek, Tom Louis, and Warner North (affiliations are given in Appendix II.)

utilitarian terms. In between, there is the use of Bayesian logic to structure analysis of problems and Bayesian statistics to draw quantitative inferences from numerically encoded information. This workshop focused on the two latter topics. Health risk assessment practices are already firmly based in science, so reinterpreting these methods in Bayesian terms seemed to offer little of substance to the issue of improving methods in this area. At the other extreme, application of Bayesian methods to *decisionmaking* poses the very difficult problem of ascertaining the values of those affected by decisions, a necessary input. The workshop advisory committee concluded that health risk assessment, particularly dose–response assessment, can benefit from infusion of Bayesian logic and, under appropriate circumstances, the use of Bayesian statistical methods.

Summaries of Faculty Presentations

Following introductory remarks by **James Wilson** (RFF) and **William (Bill) Farland** (EPA), who set out EPA's objectives, **Tom Louis** (RAND Corporation) described Bayesian logic and statistics and their use in informing conclusions. He explained that conclusions based on statistical analyses can depend on how questions are framed, illustrating his point with some examples drawn from toxicological and medical literature. He contrasted Bayesian and conventional statistical ("frequentist") approaches, and the consequences for experimental design. From an appropriate Bayesian design, more information can often be obtained with a particular input of resources. He concluded that, in general, using Bayesian logic permits greater flexibility but demands more thought in the beginning stages.

Kevin Brand (University of Ottawa) compared and contrasted several computational approaches used for approximating a posterior distribution. Most useful when closed-form (conjugate prior-based) expressions for the posterior distribution are unavailable (the more general case), these approaches were classified into noniterative and iterative approaches. Noniterative approaches were further classified into direct (for example, Monte Carlo Integration) and indirect methods, including importance sampling, sampling importance resampling, and acceptance rejection sampling. He described the steps involved in each of these procedures and demonstrated them on two simple problems in regulatory toxicology. He then introduced a promising and publicly available Windows program called WinBUGs, which implements Bayesian inference using Gibbs sampling (an iterative approach). He then briefly demonstrated the software, highlighting the software's use of "directed graphs" in structuring the logic of the analysis.

Warner North (NorthWorks), a long-time practitioner of risk and decision analysis, described two applications to case studies: one involving public policy on weather modification, and the other involving microbial contamination on a National Aeronautics and Space Administration spacecraft. His examples illustrated the usefulness of Bayesian analysis for gaining insight into which uncertainties are most important and evaluating how uncertainties can be reduced by further research and experimentation.

Donald Berry (University of Texas, M.D. Anderson Cancer Center) described some of his work in using Bayesian statistics to design and interpret drug trials. He repeated Louis's statement that Bayesian study designs allow maximal use to be made of limited resources—in his case, patients in drug trials. Berry claimed that using Bayesian analysis allows the key parameters in drug design and testing to be obtained sooner and with less risk to patients.

The first day closed with an exercise in estimating prior knowledge led by **Alison Cullen** (University of Washington).

The workshop's second day was devoted to illustrating uses of Bayesian analysis in risk analysis. **Mitchell Small** (Carnegie Mellon University) described some of his work done to estimate exposures. He showed how Bayesian methods can be used to refine a map of how differing treatment technologies for arsenic in water are distributed across the country. A workshop participant commented that this analysis makes an important contribution to risk management models for arsenic contamination. **Igor Linkov** (Menzie-Cura & Associates) described application of Bayesian techniques for model calibration. He presented a model that estimates the bioaccumulation of pollutants in different reaches of a stream. The model calibrated using experimental data collected in one reach provided understanding of other target areas. Bayesian calibration techniques can be used to incorporate limited amounts of uncertain data in modeling.

Anthony (Tony) Cox (Cox Associates) gave a well-received lecture on use of Bayesian methods, focusing on his work on inferring causality from epidemiological study results. He introduced the use of a technique called "causal graphs" that both facilitates the analysis of and clarifies relationships among variables that feature complex interactions.

Daniel (Dan) Byrd (CTRAPS) followed by describing use of a Bayesian analysis to infer the location of a threshold in cancer risk from arsenic exposure. The day closed with a panel discussion by Byrd, Cox, North, and **Harvey Richmond** (EPA) focussing on issues in the use of Bayesian approaches in dose–response analysis.

The third day began with **Annie Jarabek** (U.S. EPA) describing how use of Bayesian analysis clarifies the presentation of regulatory risk analysis results and associated uncertainties and facilitates complex analyses, that is, drawing inferences from apparently conflicting data sets.

The day concluded with a panel consisting of Jarabek, **James Cogliano** (EPA), **Adam Finkel** (U.S. Occupational Safety and Health Administration), **Mark Youngren** (Mitre Corporation), and **Lauren Zeise** (California EPA) and facilitated by **Donald Barnes** (EPA). This panel discussed barriers to the introduction of new methods and technologies and ways these barriers might be overcome. Their observations and suggestions are summarized below.

Feedback from participants indicated that one of the sponsors' goals was met: audience members reported that they gained an expanded understanding of Bayesian logic and statistics, their utility, and the diversity of present applications.

Significant Findings

Bayesian Approaches Can Improve Risk Analysis Practices

Participants in the workshop agreed that wider use of Bayesian approaches can improve human health risk assessment practices. Areas judged to pose most significant opportunities include

- estimating exposure–response functions;
- inferring causality, especially when interpreting results of epidemiological studies; and

- performing complex exposure assessments.

Conventional health risk assessment derives from the method developed some 50 years ago to evaluate the safety of chemicals used as food additives. Although this method was based on sophisticated biology and serves us very well in appropriate applications, its limitations burden its progeny. These are not sophisticated analytical tools. Practitioners in the field are increasingly coming to realize that many important decisions are not adequately informed by assessments done using these derived methods. The need for better analytical methods is particularly acute in the evaluation of dose–response functions. Current methods are not able to make use of a wealth of data that can be generated using tools of modern biochemistry and molecular genetics.

One of the most pressing needs facing risk assessment practitioners is estimating responses that are small but not zero. What are we to make of exposures that exceed levels judged safe, but not by enough for toxicologists to conclude that the exposures are actually harmful? The proper measure for this would be the probability of injury or harm, given exposure. This metric requires identification of a true dose–response relationship and precise evaluation of associated parameters. Workshop participants agreed that Bayesian methods are particularly appropriate for this kind of task.

Inferring causality from epidemiological study results presents possibly the most contentious process within the subdiscipline. Bayesian analytical methods permit much more precise and robust conclusions concerning causality than do conventional methods.

Bayesian approaches have begun to be applied to assessments of exposure for both human health and environmental risks. Two very different applications of this kind were presented in the workshop. Use of Bayesian approaches brings to exposure assessment many of the same kinds of advantages expected for dose–response assessment: more effective use of diverse data, more robust conclusions, and a better understanding of uncertainties.

Barriers to Acceptance of Bayesian Methods Exist and Can Be Overcome

Workshop participants identified several barriers to acceptance of Bayesian approaches in dose–response assessment and suggested several approaches to overcoming those barriers. They are summarized here.

Existing Barriers to Acceptance

- Policymakers' reluctance to depart from previous practices
- Simple inertia (on the part of analysts)
- Fear of how new methods will be viewed by the public ("How will it play in Peoria?")
- Criticism stemming from the discovery of uncertainties in the old methods
- Uncertainties about whether new methods will be applicable in practice
- Uncertainty about what constitutes an "adverse effect"

Suggestions for Overcoming These Barriers

- Develop champions for new methods among the affected technical community

- Integrate new methods into ongoing business; apply them to solve serious problems
- Develop arguments that will support and promote the concept that change brings benefits and improves on existing practices
- Choose first uses carefully, and attempt to avoid disasters
- Work to achieve buy-in among affected groups; demand-pull marketing is vital
- Obtain peer review as development progresses

All the barriers identified—save the last—commonly hinder innovations of the kind of interest here, adopting Bayesian methods for use in dose–response assessment. They occur in almost every organization whenever some process change is being advocated or considered. They follow from some common human traits, including fear of the unknown, fear of loss of power, and fear of criticism. Typically, organizational innovations are successful when they are strongly backed by someone (or a group) with high status in the organization, whether formal or informal. They can be people who lead by example, showing their fellows that using the new ways makes life easier or allows something to be done that previously was nearly impossible.[4] The suggestions for overcoming the barriers reflect this experience.

The last barrier identified, uncertainty about what constitutes an "adverse effect," is both specific to our discipline and an issue with rather broad ramifications within the practice of regulatory risk assessment. Most regulations focus on preventing harm (although that thought may be expressed in any of several different ways). About three decades ago, the notion of "harm" became associated with a term of toxicologist's art, "adverse effect." Once upon a time, there existed a broad consensus on the kinds of responses in test animals observed to follow chemical treatment that should be considered "adverse"; it focused on death and serious illnesses such as cancer and skeletal deformities in test animals' offspring. In recent years, however, advances in biochemistry, molecular biology, and genetics have provided toxicologists with tools that can identify small changes in treated animals. Some of these responses, such as the induction of detoxifying enzymes, are generally considered to be "adaptive"—that is, changes that will disappear without permanent harm to the animal were chemical treatment to be discontinued. But for many analysts, the meaning is ambiguous. This ambiguity poses something of a barrier to estimating exposure–response functions: which responses should be considered?

Recommendations

The workshop participants voiced several suggestions for promoting use of Bayesian analysis in dose–response assessment.

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[4] For two scholarly views of this process, see books by R.M. Kanter [*The Change Masters: Innovation and Entrepreneurship in the American Corporation.* New York: Simon and Schuster (1983)] and by C. Argyris and D.A. Schön [*Theory in Practice: Increasing Professional Effectiveness.* San Francisco CA: Jossey-Bass Publishers (1974)].

1. EPA, other regulatory agencies that use dose–response assessment as part of their processes, and the private sector all should take steps to foster the use of Bayesian approaches.
2. EPA and other agencies should work to persuade professional societies (for example, Society for Risk Analysis, Society of Toxicology) to seek out and recognize meritorious analyses that use Bayesian approaches.
3. EPA and private-sector organizations should consider sponsoring research into using Bayesian approaches, demonstrating analyses that use them, and using the results of this work to help educate peers in the risk analysis and toxicology professions.
4. EPA should request all staff and contractor scientists who develop mathematical models to use Bayesian techniques to calibrate models. This is the least controversial and most straightforward application of Bayesian logic.
5. EPA should consider ways to inform its staff, contractors, and the research community as to the utility of Bayesian analyses. In particular, EPA might consider the following suggestions:
    - Invite proposals for research into components of a general method for conducting Bayesian-based exposure–response assessment.
    - Identify the substances for which having good, relatively accurate exposure–response functions available might impact policy decisions. Such knowledge would provide EPA and other researchers with leads toward useful research.
    - Give consideration to the value of internal training in the basics of Bayesian logic and statistics.
6. EPA should consider improving its research planning by making use of Bayesian techniques (including value-of-information analyses). Doing so would allow the agency to understand the relative importance of different topics and to help target research projects and programs toward those that will enable more accurate assessments of the consequences of environmental policies.

Appendix I: Agenda

September 18

8:30 A.M.	Registration	
9:00 A.M.	WELCOME (and administrative)	James D. Wilson (RFF)
9:15 A.M.	INTRODUCTION: *Purpose and Importance of the Workshop*	William Farland (EPA)
9:45 A.M.	LECTURE: *Theory of Bayesian Logic and Statistics*—introduce concepts, illustrate range of uses, describe limitations	Thomas Louis (RAND Corp.)
10:30 A.M.	Break	
10:45 A.M.	DEMONSTRATION: *Using Readily-Available Software to Compute Posteriors, Given Appropriate Input*	Kevin Brand (U. Ottawa)
11:45 A.M.	Lunch	
1:00 P.M.	LECTURE: *Applying Bayesian Logic in a Decision Context*—review theory, describe application to relevant decisions	W. North (NorthWorks)
1:45 P.M.	Discussion and questions	Panel
2:00 P.M.	LECTURE: *Use of Bayesian Approaches In Medical Research—Clinical Trials*—illustrate use, need to identify appropriate priors	Donald Berry (U. of Texas, M.D. Anderson Cancer Center)
2:45 P.M.	Discussion and questions	
3:00 P.M.	Break	
3:15 P.M.	EXERCISE: *Identifying Inputs*	Alison Cullen (U. of Washington), leader
5:15 P.M.	PLENARY: Discuss exercises, what was learned	Panel
6:00 P.M.	Adjourn for the day	

September 19

8:45 A.M.	PLENARY: Plan for the day, questions	
9:00 A.M.	LECTURE: *Using Disparate Data in Exposure Assessment*	Mitchell Small (Carnegie Mellon U.)
9:45 A.M.	Discussion and questions	
10:00 A.M.	Break	
10:15 A.M.	DEMONSTRATION: *Application to ecological risk*—illustrate use, illustrate how to deal with errors in data	Igor Linkov (Menzie-Cura & Associates)
11:30 A.M.	Discussion and questions	Panel
11:45 A.M.	Lunch	
1:00 P.M.	LECTURE: *Bayesian Risk Assessment: Combining Evidence from Multiple Sources*	L. Anthony Cox (Cox Associates)
1:45 P.M.	Discussion and questions	
2:00 P.M.	DEMONSTRATION: *Constructing an Exposure–Response Function*	Daniel Byrd, (CTRAPS)
2:45 P.M.	Discussion and questions	
3:00 P.M.	Break	
3:15 P.M.	PANEL DISCUSSION: *Issues in Estimating Dose–Response Functions*	Panelists

	PLENARY: *General Discussion*	
5:00 P.M.	Adjourn for the day	
	September 20	
8:30 A.M.	DEMONSTRATION: *Bayesian Applications in Routine Regulatory Risk Assessment*	Annie Jarabek (EPA)
9:15 A.M.	Discussion and questions	
9:30 A.M.	PLENARY: Review of exercises, questions, and discussion	J. Wilson and A. Jarabek
10:15 A.M.	Break	
10:30 A.M.	PANEL DISCUSSION: *Where Do We Go from Here? Applications and Research Needs*	Donald Barnes (EPA) and panelists
12:00 noon	Adjourn (lunch provided)	

Appendix II: Faculty and Panelists

Faculty

DONALD BARNES, U.S. EPA, Washington, DC

DONALD BERRY, University of Texas, M.D. Anderson Cancer Center, Houston, TX

KEVIN BRAND, University of Ottawa, Ottawa, Ontario, Canada

DANIEL BYRD, CTRAPS, Washington, DC

L. ANTHONY COX, Cox Associates, Denver, CO

ALISON CULLEN, University of Washington, Seattle, WA

WILLIAM FARLAND, U.S. EPA, Washington, DC

ANNIE JARABEK, U.S. EPA, Research Triangle Park, NC

IGOR LINKOV, Menzie-Cura & Associates, Chelmsford, MA

THOMAS LOUIS, RAND Corporation, Arlington, VA

WARNER NORTH, NorthWorks, Belmont, CA

MITCHELL SMALL, Carnegie Mellon University, Pittsburgh, PA

Panelists

DANIEL BYRD

JAMES COGLIANO, U.S. EPA, Washington, DC

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ADAM FINKEL, U.S. OSHA, Washington, DC

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Appendix IV: Some Electronic Sources of Information[5]

http://bayes-an@xxx.lanl.gov—The bayesian repository is a project of the International Society for Bayesian Analysis. It is a fully automated e-print archive (starting from June 1, 1995) intended for papers that use or develop Bayesian methods of statistical inference. Appropriate topics include but are not limited to computational techniques, computer programs, control theory, decision analysis, empirical Bayes, entropy/maxent, estimation, forecasting/prediction, historical studies, information theory, invariance, model formulation, model selection, mathematical methods, nonparametrics and semiparametrics, prior distributions, robustness, sequential analysis, signal and image processing, testing, and theory/foundations. Specific applications of Bayesian methods to diverse fields such as medicine, law, physical sciences, economics, agriculture, marketing, and engineering are also appropriate. Internet access is available via this URL. To communicate with the archive via e-mail, send messages to bayes-an@xxx.lanl.gov. Anonymous ftp access is available via xxx.lanl.gov

http://www.bayesian.org/—The International Society for Bayesian Analysis (ISBA) was founded in 1992 to promote the development and application of Bayesian statistical theory and methods useful in the solution of theoretical and applied problems in science, industry, and government. By sponsoring and organizing meetings and other activities, ISBA provides a focal point for those interested in Bayesian inference and its applications. The function of the website is to serve as a resource for members of ISBA and for the larger community of individuals who have an interest in Bayesian statistics.

http://www.informs.org/society/da—DAWeb is the website of the Decision Analysis Society of INFORMS. The society promotes the development and use of logical methods for the improvement of decisionmaking in public and private enterprise. Such methods include models for decisionmaking under conditions of uncertainty or multiple objectives, techniques of risk analysis and risk assessment, experimental and descriptive studies of decisionmaking behavior, economic analysis of competitive and strategic decisions, techniques for facilitating decisionmaking by groups, and computer modeling software and expert systems for decision support.

http://www.stat.ucla.edu/~jsanchez/sbssnews/history/history.html—The Section on Bayesian Statistical Science (SBSS) of the American Statistical Association (ASA) reflects a need for statisticians and people from other disciplines who have interests in the Bayesian paradigm to formalize their common interests within the statistical community represented by ASA. Some of the people interested in forming such a section had already clustered together over the years in small special interest groups relating to Bayesian statistics. It was their hope that the ASA SBSS would provide a common focus for these groups, as well for the wider scientific community.

[5] The author is indebted to D.M. Byrd for providing this listing.

http://www.statslab.cam.ac.uk/~mcmc/—The Markov Chain Monte Carlo Preprint Service.

http://dimacs.rutgers.edu/~dbwilson/exact.html/—The "perfectsimulation" home page: "Perfectly Random Sampling with Markov Chains."

http://www.mrc-bsu.cam.ac.uk/bugs/welcome.shtml—The BUGS project (Bayesian inference using Gibbs sampling) is a piece of computer software for the Bayesian analysis of complex statistical models using Markov chain Monte Carlo (MCMC) methods. It grew from a statistical research project at the MRC Biostatistics Unit but now is developed jointly with the Imperial College School of Medicine at St. Mary's, London.

http://bayes.stat.washington.edu/bayes_people.html—A list of websites of some Bayesian experts.

http://omega.math.albany.edu:8008/JaynesBook.html—The contents of E.T. Jaynes' book, *Probability Theory: The Logic of Science*.

Appendix V: Suggested Reading

Berry, Donald A., and Dalene K. Stangl (eds.). *Bayesian Biostatistics.* Marcel Dekker, New York (1996).

Carlin, Bradley P., and Thomas A. Louis. *Bayes and Empirical Bayes Methods for Data Analysis.* Chapman & Hall, London (2nd Edition, 2000).

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Igor Linkov, D. Burmistrov, M. Kandlikar, and William R. Schell. Reducing uncertainty in the radionuclide transport modeling for the Chernobyl forests using Bayesian updating. In *Contaminated Forests,* edited by I. Linkov and W.R. Schell. Kluwer Academic Publishers, Amsterdam, the Netherlands (1999), pp. 143–150.

Morgan, M. Granger, and Max Henrion. *Uncertainty: A Guide to Dealing with Uncertainty in Quantitative Risk and Policy Analysis.* Cambridge University Press, Cambridge, U.K. (1990), especially Chapters 6 and 7.

North, D. Warner. Risk assessment using the Taiwan data base: The need for further research. *Human and Ecological Risk Assessment* **4**: 1051–1060 (1998).

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Schafer, J.L. *Analysis of Incomplete Multivariate Data*. Chapman & Hall, New York (1997).

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Tversky, Amos. Assessing uncertainty (with discussion). *Journal of the Royal Statistical Society Series B* **36**: 148–159 (1974).